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Bilateral Porencephaly, Cerebellar Hypoplasia, and Internal Malformations: Two Siblings Representing a Probably New Autosomal Recessive Entity

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We report on 2 sibs with bilateral porencephaly, absence of the septum pellucidum, and pancerebellar hypoplasia including absence of the vermis. Situs inversus and tetralogy of Fallot was present in one, and an atrial septal defect in the other. This constellation of findings is discussed against the background of familial porencephalies and schizencephalies, familial cerebellar hypoplasias, and asplenia/polysplenia syndromes. It is concluded that the described constellation of findings constitutes a new entity of probably autosomal recessive inheritance. © 1996 Wiley-Liss, Inc.

KEY WORDS: familial porencephaly, "basket brains," cerebellar hypoplasia, situs inversus, tetralogy of Fallot, autosomal-recessive inheritance

INTRODUCTION

Porencephalies are apparently disruptive lesions of the developing brain which may occur in isolation or rarely in association with other syndromic anomalies. These lesions are sporadic in most cases, although familial cases have been described. Cerebellar hypoplasia and agenesis of the vermis are viewed as dysplasias, again with possible sporadic, familial, and syndromic occurrence. In the sibs reported in this paper these two types of CNS abnormalities are seen together in addition to internal anomalies. The familial observation strongly suggests a genetic cause of this syndrome.

CLINICAL REPORTS

The parents were of Turkish ancestry and were first cousins. Patient 1, a boy, was their first child. The second child was a healthy boy, after which patient 2, a girl, was born.

Patient 1

The boy was born at 37 weeks of gestation after an uncomplicated pregnancy without known drug or toxin exposure. His length at birth was 50 cm. Mild macrocephaly and hypertelorism were noted (Fig. 1), the alveolar ridges were broad, and the palate was highly arched. Subsequent investigations disclosed tetralogy of Fallot and total situs inversus. His left pupil was ovally shaped; ophthalmologic evaluation did not demonstrate any further abnormalities. A computed tomography (CT) scan of the head demonstrated massive hydrocephalus with bilateral cortical defects, absence of the septum pellucidum, cystic dilatation of the fourth ventricle, and cerebellar hypoplasia without recognizable vermis (Fig. 2). G-banded chromosomes on cultured lymphocytes showed a normal male karyotype. The infant went on to show severe developmental delay and died at home of heart failure. Autopsy was refused by the parents.

Patient 2

Routine sonography of the fetal head during week 32 of the mother's third pregnancy demonstrated enlarged ventricles. At 39 weeks of gestation a female infant was delivered spontaneously. Her length was 46 cm (−2 SD), her weight was 2,700 g (−1.6 SD), and her head circumference was 34.5 cm (mean). Apgar scores were 9 and 10 at 1 and 5 min, respectively. On examination her face was mildly abnormal with a prominent metopic suture, bilateral epicanthus, and a highly arched palate (Fig. 3). Investigations disclosed a small atrial septal defect (ASD). A magnetic resonance imaging (MRI) scan of the brain showed hydrocephalus with asymmetric expansion of the ventricles, absence of the septum pellucidum, and extensive bilateral cortical defects. Cerebellar hypoplasia with agenesis of the vermis was seen, but there was no cystic expansion of the fourth ventricle (Fig. 4a–c). A G-banded karyotype from cultured lymphocytes was normal. The infant had low muscle tone and feeding difficulties. At age 5 weeks accelerated head growth necessitated the insertion of a ventriculoperitoneal shunt. On ophthalmologic exami-

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Fig. 1. Patient 1. Note mild macrocephaly and hypertelorism as the only abnormal findings.

nation, corneal clouding and a pale optic nerve head were noted. At age 2 months seizures occurred, with a multifocal slow wave and spike pattern, at times resembling hypsarrhythmia on electro encephalography (EEG). Subsequent development was severely retarded, and hypertonia with hyperactive deep tendon reflexes and positive Babinski signs were noted on neurological examination.

DISCUSSION

We report on 2 sibs with bilateral porencephaly and hydrocephalus, resulting in a "basket-like" appearance of the brain. Both sibs had posterior fossa malformations with severe cerebellar hypoplasia and apparent absence of the vermis. Cystic dilatation of the fourth ventricle, resembling Dandy-Walker malformation, was present in patient 1. There was no cystic dilatation of the fourth ventricle in the second patient. Additional abnormalities included situs inversus and tetralogy of Fallot in patient 1, and an atrial septal defect in patient 2. Both children were severely retarded; longer survival in the second sib was associated with the development of seizures and corneal clouding.

Porencephalies are prenatally acquired defects of the cerebral mantle. They can vary in severity from complete "destruction" of the hemispheres, resulting in hydranencephaly, to incomplete forms such as focal polymicrogyria [Barkovich and Kjos, 1992]. Uni- and bilateral forms occur, and may be of varying extent on the two sides. The pathological appearance is partly related to the developmental timing of the insult. Lesions that occur prior to the completion of neuronal migration may be associated with abnormalities of cortical organization and migrational disturbances in the vicinity of the defect or in the lining of the pore. Lesions occurring between about 18–22 weeks of gestation can be associated with polymicrogyria at the edge of the defect. Polymicrogyria can also be the only abnormality without a concomitant pore. Glial scarring at the site of the defect may occur after 20 weeks of gestation [Friede, 1989]. Porencephalic defects can expand and cause compression of the adjacent parenchyma. In cases of extensive bilateral porencephalies the term "basket-brain" [Obersteiner, 1902; Friede and Mikotasek, 1978] has been coined, referring to the re-

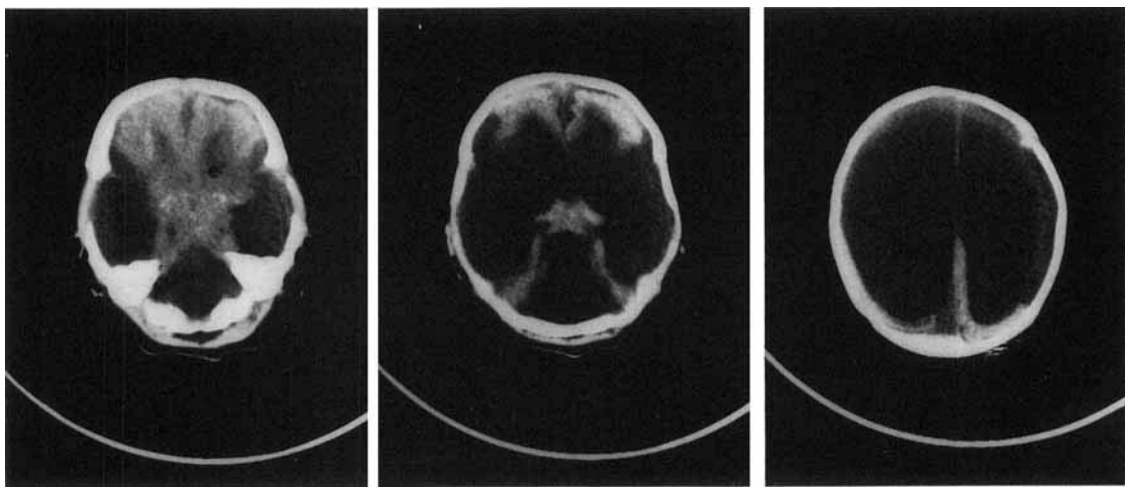

Fig. 2. CT scan of the brain, patient 1. Note large bilateral hemispheric defects, enlarged ventricles, absence of the septum pellucidum, hypoplasia of the cerebellum with aplasia of the vermis, and cystic expansion of the posterior fossa.

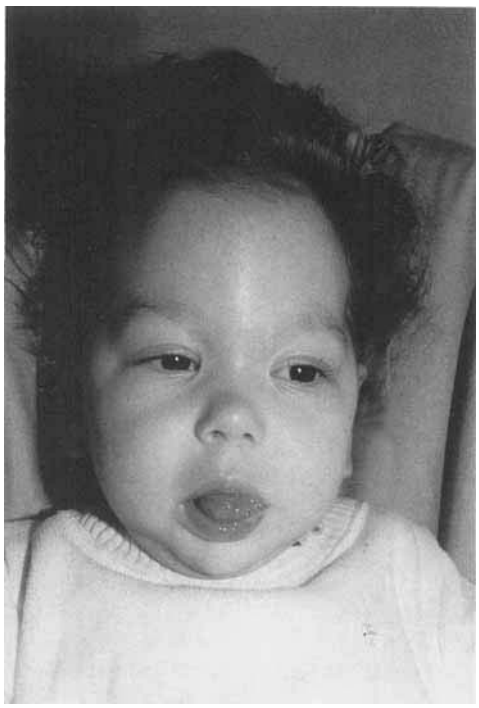

Fig. 3. Patient 2. Note prominent metopic suture and bilateral epicanthus as the only mildly abnormal findings.

maining parasagittal tissue, giving the brain the appearance of a basket with a handle. The topography of the insult often resembles the territory of the middle cerebral artery, suggesting a vascular cause for this disruptive insult. Inflammatory conditions have also been implicated.

The term schizencephaly was initially meant to designate a primary developmental defect of hemispheric formation ("clefting") [Yakovlec and Wadsworth, 1964]. However, it has become increasingly clear that like porencephaly, schizencephaly can also result from apparent disruptive insults to the developing hemispheres, though possibly at a generally earlier gestational age [Barkovich and Kjos, 1992]. It shares many of the pathological findings described for porencephaly. There currently is considerable disagreement about whether these two terms should be kept separately or merged under the heading of porencephaly as part of the same disruptive spectrum [Sarnat, 1992a; Friede, 1989]. For ease of evaluation of the literature, we will use in the following discussion the terms porencephaly and schizencephaly separately.

Most cases of porencephaly appear to be sporadic, and some occur in the setting of exposure to teratogens, leading to vascular insults (e.g., cocaine and amphetamines [Dominguez et al., 1991]), or in the setting of increased risk for vascular events during pregnancy (e.g., twin pregnancies or autoimmune thrombocytopenic purpura in the mother [Jung et al., 1984; Friedman and Aster, 1982]). Evidence for more extensive disruptive pathology can be seen in some cases (e.g., absence of the septum pellucidum [Aicardi and Goutières, 1981]), hydranencephaly [Friede, 1989], and fetal brain disruption sequence [Russel et al., 1984; Bönnemann and Meinecke, 1990]).

Cases of familiar occurrence of porencephaly have been reported [Shastri et al., 1993; Herranz Fernandez et al., 1992; Sensi, 1990; Zonana et al., 1986; Airaksinen, 1984; Smit et al., 1984; Berg et al., 1983]. Affected individuals present most commonly with combinations of hemiparesis, mental retardation, and seizures. The family described by Haar and Dyken [1977], with symptoms of a "hereditary athetotic hemiplegia" and unilateral ventricular enlargement with hemispheric atrophy, can probably be included in the same group of diseases. Imaging (mostly CT) revealed isolated porencephalic defects of varying degrees, the severity of which may be variable in members of the same family. No associated malformations of the brain or other organs were reported in these families. For most families, autosomal dominant inheritance with varying expressivity is assumed due to the occurrence of one affected parent, or due to clinical or radiological evidence of porencephaly in other family members. The family reported by Shastri et al. [1993] could conceivably follow autosomal recessive inheritance. The pathogenesis of defects is unclear in all families reported.

Familial cases of "schizencephaly" have also been described. Clinically the presentation is indistinguishable from the porencephalies described above. The families of Tilton et al. [1988], Robinson [1991], and Haverkamp et al. [1995] suggest autosomal recessive inheritance, though more extensive family information as well as imaging of the parents is not available. In the family reported by Hosley et al. [1992], the same mother has 2 affected children of different sexes with 2 different partners. This would suggest autosomal dominant or mitochondrial (maternal) inheritance. Again, imaging is not available in the mother, but even if she was found to be normal, germline mosaicism or variable penetrance would need to be excluded.

Familial hydranencephaly was described by Harper and Hockey [1983]. Two sibs with hydranencephaly and the finding of a "proliferative perithelial vasculopathy" at autopsy were reported. Tissue destruction secondary to ischemia resulting from the proliferative vasculopathy was proposed as a pathogenetic mechanism, and autosomal recessive inheritance was suggested. Najafzadeh et al. [1982] described 2 sibs born to consanguineous parents. Both had hydranencephaly, but in addition showed small remnant (appendage-like) cerebelli, small or aplastic optic and olfactory nerves, microcephaly, hypotelorism/microphthalmia, and multiple joint contractures. Again, autosomal recessive inheritance was most likely and the pathogenesis was unclear, although a vascular disruptive event was thought to be likely.

Porencephaly can also be seen in syndromes of mesenchymal and epidermal harmatomatous maldevelopment, such as encephalocraniocutaneous lipomatosis [Fishman, 1987], the epidermal nevus syndrome [Baker et al., 1987], and the oculocerebrocutaneous (Delleman) syndrome [Bleeker-Wagemaker et al., 1990]. Some form of vascular dysplasia could conceivably be underlying these cases.

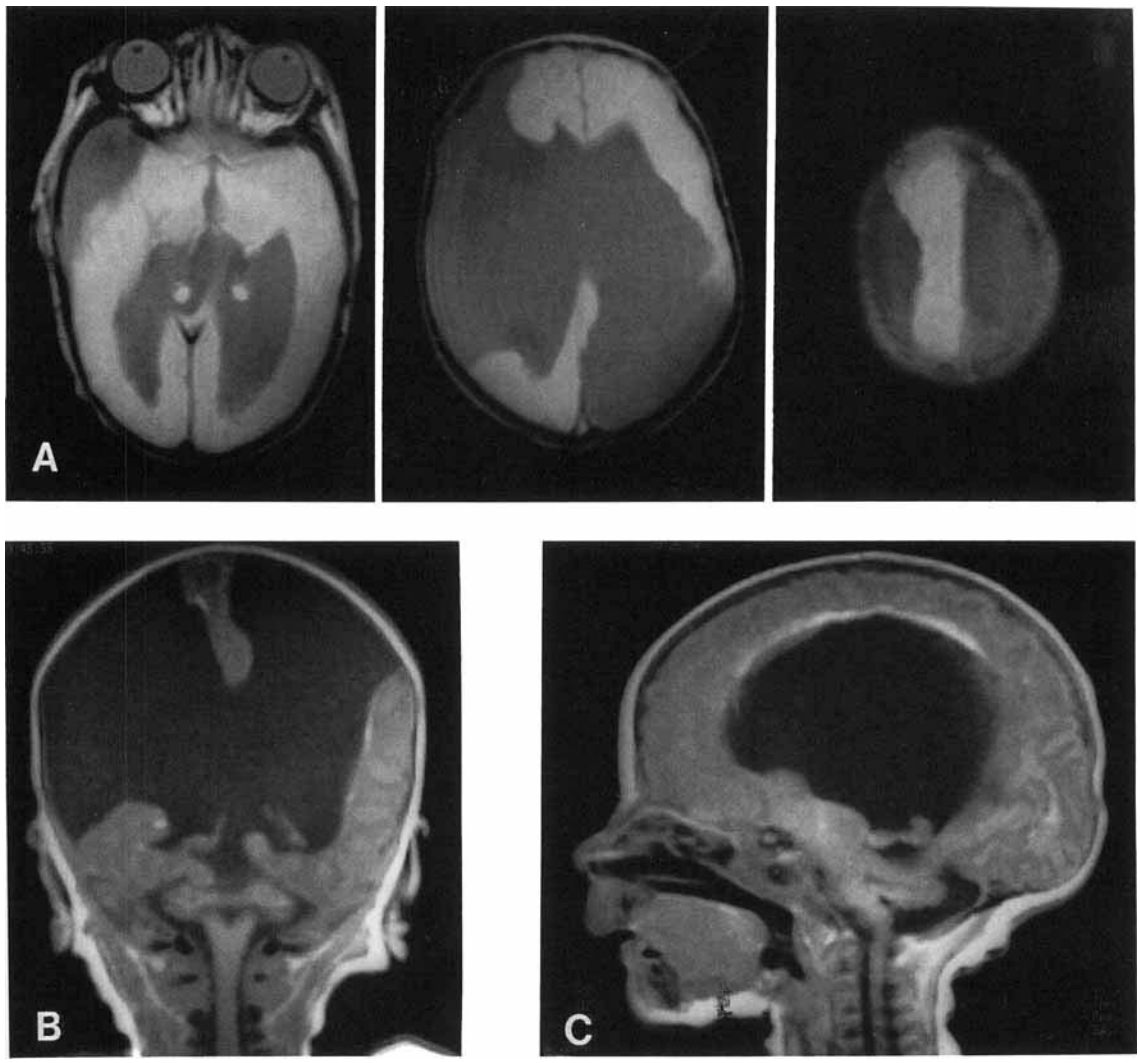

Fig. 4. Axial (**a**), coronal (**b**), and sagittal (**c**) T1-weighted magnetic resonance images of the brain, patient 2. Note bilateral hemispheric defects with enlarged ventricles, absence of the septum pellucidum, and cerebellar hypoplasia with aplasia of the vermis, but without cystic expansion of the posterior fossa. Also note preservation of parasagittal tissue on the coronal image (b).

In addition to extensive bilateral porencephalies, our cases also showed posterior fossa abnormalities consisting of pancerebellar hypoplasia with agenesis of the vermis, with or without a Dandy-Walker type cyst. The wide variety of monogenic, chromosomal, and syndromic conditions in which cerebellar hypoplasia (panhypoplasias or selective hypoplasia of the cerebellar vermis) and/or the Dandy-Walker malformation can occur, precludes a detailed discussion of these entities in the context of this report. Excellent reviews have been provided by Macchi and Bentivoglio [1987], Bordarier and Aicardi [1990], Bruyn [1991], and Sarnat [1992b]. Porencephalic defects are not a finding in these disorders, and none of these clinical constellations appear to resemble the cases under discussion.

However, cases with a combination of posterior fossa and telencephalic abnormalities need to be differentiated from Walker-Warburg syndrome [Dobyns et al., 1989], which consists of a combination of agyria or polymicrogyria, hydrocephaly, cerebellar malformations, and congenital muscular dystrophy. In our cases there is no evidence on neuroimaging studies of an argyric lissencephalic or polymicrogyric cortex, though the CT in case 1 is not sufficient to rule out this possibility. Porencephalic defects have not been described in Walker-Warburg syndrome. In a recent review by Altman et al. [1992] of posterior fossa malformations, a patient with a Dandy-Walker malformation, cerebral agyria/pachygyria, absent septum pellucidum, and bilateral cortical clefts ("schizencephaly") was reported. The girl also had external auditory atresia and low-set malformed pinnae. No further clinical information was provided, and the nosological status of that patient remains unclear. Aicardi syndrome can also be associated with cerebellar and telecephalic malformations [Donnenfeld et al., 1989]. In addition to the typical findings of chorioretinal lacunae, callosal agenesis, and vertebral anomalies, a variety of other central nervous sys-

tem (CNS) malformations can be seen. These include cerebellar vermis hypoplasia as well as cerebellar hemispheric dysplasia in the posterior fossa, and hippocampal anomalies, heterotopias, and polymicrogyria in the telencephalon [Ferrer et al., 1986]. In a number of cases, unilateral ventriculomegaly suggesting incomplete porencephaly has been seen [Donnenfeld et al., 1989]. However, the anomalies described above and their almost exclusive occurrence in girls exclude Aicardi syndrome from the differential diagnosis of our cases.

Situs inversus has been described in association with central nervous system defects including hydrocephalus, meningocele, and arrhinencephaly. Cerebellar hypoplasia has been observed in a family with X-linked laterality sequence [Mathias et al., 1987], and also in earlier series of the asplenia/polysplenia syndrome [Freedom, 1972; Chandra, 1974]. The affected boy in the family of Mathias et al. [1987] also had tetralogy of Fallot, thus resembling our first case somewhat, except for the different and more severe CNS findings in our case. The cerebellar hypoplasia in these patients (total of 5) is described as "mild-to-moderate." In one patient [Freedom, 1972], a parietotemporal porencephalic cyst is mentioned; no other details about this patient are given.

The cerebral malformations in our cases represent a combination of a developmental dysgenesis (cerebellum) with a disruptive event (porencephaly). Only in the hydranencephalic cases of Najafzadeh et al. [1982] can such a combination of disruptive and dysplastic pathology be found. However, these cases are clearly different from ours. It is interesting to note that Pascual-Castroviejo [1978] reported vascular hypoplasias of the posterior circulation in cases of cerebellar hypoplasia. In pancerebellar hypoplasia he also observed additional vascular abnormalities such as persistent fetal vessels (trigeminal artery), as well as dysplastic large vessels in the anterior circulation. Thus, it is tempting to speculate that a unifying error of vascular development may result in dysgenesis as well as disruption. The major cerebral vessels form around 7–8 weeks of gestational age from the third aortic arch. At this time the cerebellar plates have formed but have not yet reached the midline to form the vermis. At the same time in development, the conotruncal septum closes, and aberration of that process may play a part in the pathogenesis of tetralogy of Fallot. Abnormalities of mesenchymal cell migration around that time of development could possibly be implicated in both of these pathogenetic processes, as well as in the occurrence of situs inversus.

In conclusion, we present a pair of sibs with bilateral porencephalies ("basket brains"), cerebellar hypoplasia with absent vermis, cardiac malformations, and situs inversus (in patient 1). To our knowledge, this combination of findings has not been reported in the setting of either familial porencephalies or of familial cerebellar hypoplasia. Cases of laterality sequence/asplenia/polyasplenia syndrome with cerebellar hypoplasia, while being different in other aspects, show some interesting resemblances to our cases [Freedom, 1972; Chandra, 1974; Mathias et al., 1987], and possibly link aspects of development of both asymmetry as well as the CNS.

Finally, given the occurrence of this syndrome in sibs of opposite sex born to consanguineous healthy parents, autosomal recessive inheritance seems most likely. However, since the parents could not be examined with neuroimaging techniques, an asymptomatic carrier status of one of the parents, and therefore autosomal dominant transmission with variable penetrance, cannot be completely excluded.

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